UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MONTY KRIEGER, and SUSAN L. ACTON[1]

Appeal No. 2005-0339
Application No. 08/765,108

HEARD: March 8, 2005

Before WILLIAM F. SMITH, SCHEINER and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 11-13, 19-22 and 44-50. The examiner

[1] This application was before this Merits Panel in Appeal No. 2001-1495. While there was a substantial amount of confusion regarding the inventorship of the claimed subject matter in Appeal No. 2001-1495, Patent Office records indicated that the inventors of the claimed subject matter were Monty Krieger, Susan L. Acton and Attilio Rigotti. On remand to the examiner, this panel required, inter alia, that the inventorship of the claimed subject matter be clarified. See Appeal No. 2001-1495, bridging paragraph, pages 5-6. In this regard, we note that in the Non-final Office action dated March 5, 2002, the examiner stated:

> IV) In view of the papers filed 23 December of 1996, the inventorship in this nonprovisional application has been changed by the deletion of Alan M. Pearson and Atilio Rigot[t]i.
>
> The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

It does not, however, appear that the PTO records have been updated to reflect the corrected inventorship. Accordingly, prior to any further action on the merits, we encourage the examiner to insure that the inventorship of this application is correctly reflected on this record. Based on the foregoing, our deliberations have proceeded with the understanding that the inventors of the claimed subject matter are Monty Krieger and Susan L. Acton.

indicated that the only other pending claims remaining, claims 14 and 15, are allowable. See Final Rejection, mailed February 19, 2004.

Claims 11, 19, 21 and 49 are illustrative of the subject matter on appeal and are reproduced below:

11. An isolated nucleic acid molecule encoding a scavenger receptor protein type BI which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, wherein the binding of acetylated low density lipoprotein to the scavenger receptor protein type BI is inhibited by native low density lipoprotein, and the isolated nucleic molecule hybridizes to SEQ ID N[O]s. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA molecule consisting of SEQ ID NO[s]: 3 and 7.

19. The molecule of claim 11[,] which encodes a human scavenger receptor.

21. An expression vector comprising the molecule of claim 11 encoding the scavenger receptor protein.

49. A method for inhibiting uptake of lipoprotein or lipids by adipocytes comprising

administering a compound selectively inhibiting binding of lipoprotein to the scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID N[O]s. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA molecule consisting of SEQ ID NO[s]: 3 and 7 and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, under conditions wherein the low density lipoprotein is bound to the scavenger receptor wherein the binding of acetylated low density lipoprotein to the scavenger receptor protein type BI is inhibited by native low density lipoprotein.

The references relied upon by the examiner are:

Degrave et al. (Degrave), "Cloning and structure of a mouse interleukin-2 chromosomal gene," Molec. Biol. Rep., Vol. 11, pp. 57-61 (1986)

Bowie et al. (Bowie), "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science, Vol. 247, pp. 1306-10 (1990)
Yang et al. (Yang), "Possible detection of a developmentally regulated heavy-chain variable region gene in autoimmune diseases," Proc. Natl. Acad. Sci., USA, Vol. 87, pp. 7907-11 (1990)

Calvo et al. (Calvo), "Identification, Primary Structure, and Distribution of CLA-1, a Novel Member of the CD36/LIMPII Gene Family," J. Biol. Chem., Vol. 268, No. 25, pp. 18929-35 (1993)

Ngo et al. (Ngo), Computational Complexity and the Levinthal Paradox in The Protein Folding Problem and Tertiary Structure Prediction pp. 492-95 (Kenneth M. Merz, Jr. et al., eds., Birkäuser, Boston) (1994)

Cao et al. (Cao), "Structure and Localization of the Human Gene Encoding SR-BI/CLA-1," J. Biol. Chem., Vol. 272, No. 52, pp. 33068-76 (1997)

GROUNDS OF REJECTION[2]

Claims 11-13, 19-22 and 44-50 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification fails to adequately describe the claimed invention.

Claims 11-13, 19-22 and 44-50 stand rejected under 35 U.S.C. § 112, first paragraph, as being based on an insufficient disclosure to support or enable the scope of the claimed invention.

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[2] According to the examiner (Communication, mailed June 23, 2004), "the rejection of claims 11-13, 19-22 [and] 44-50 under 35 U.S.C. [§] 112, second paragraph, as set forth beginning at page 12 of the [e]xaminer's Answer (4/704) is withdrawn in view of [a]ppellant's [sic] amendments filed 6/7/04."

Claims 11, 13, 19, 20 and 22 stand rejected under 35 U.S.C. § 102(a) as anticipated by Calvo.

Claim 21 stands rejected under 35 U.S.C. § 103 as being unpatentable over Calvo.

We reverse.

DISCUSSION

Written Description:

I. The claimed genus of nucleic acid molecules:

According to the examiner (Answer, page 3), appellants'

> specification discloses a hamster and a mouse polynucleotide of SEQ ID NO[s]:3 and 7, respectively, yet the claims encompass polynucleotides not described in the specification, i.e. polynucleotide[ ] sequences from other species, mutated sequences, allelic variants, or sequences that need only hybridize to SEQ ID NO[s]: 3 or 7 under moderately stringent conditions yet which retain the required functional limitations.[3]

Accordingly the examiner finds (Answer, page 4), "[w]ith the exception of the hamster and mouse polynucleotides referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed 'scavenger receptor protein type BI' that are not encoded by SEQ ID NO[s]: 3 or 7...."

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[3] According to appellants' specification (pages 38-39),

> the term "SR-BI" refers to the nucleotide and amino acid sequences, respectively, shown in Sequence ID N[O]s. 3 and 4, and 7 and 8, and degenerate variants thereof and their equivalents in other species of origin, especially human, as well as functionally equivalent variants, having additions, deletion, and substitutions of either nucleotides or amino acids which do not significantly alter the functional activity of the protein as a receptor characterized by the binding activity identified above.

According to appellants (Brief, page 7), "SR-BI [(scavenger receptor protein type BI)] is defined in the specification based on its three dimensional structure (see Figure 1B)[4]; amino acid sequence (SEQ ID N[O]s 4 and 8), and binding activity (binds native LDL, modified LDL when in the presence of 10% serum, and HDL)." In addition, appellants explain (Brief, page 8),

> it is possible to detect SR-BI from one species with the DNA from another. As described in the application, Northern blot analysis of murine tissues was conducted using the hamster DNA) [sic], to show that SR-BI is most abundantly expressed in fat and is present at moderate levels in lung and liver. ... Based on the tissue expression data in the application, as well as the binding data, one skilled in the art would also know that it is involved in lipid transport....

In addition, appellants assert (Brief, page 9),

> [o]nce one has the protein and the isolated DNA encoding protein, from any species, it is possible to make antibodies to the protein or hy[b]ridization probes which can be used to screen patients or tissues for expression of SR-BI in levels or with function that is not normal (claim 50); it can be used as a target in screening procedure for drugs which bind to SR-BI to alter lipid or lipoprotein uptake or transport (claims 44-47 and 49); and it can be immobilized and used to remove LDL from a patient's blood (claim 48).

In response, the examiner argues (Answer, page 18),

> the issue here is that the specification has not put forth a particular structure(s), present in each member of the vast and disparate genus claimed, that is asserted to correlate with a function. The mere recitation that the polynucleotide hybridize under moderately stringent conditions does not stipulate or describe any particular structure or function – it simply provides some constraint on the possible deviation in structure that is allowed....

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[4] We recognize the examiner's comment (Answer, bridging sentence, pages 17-18), "[a]ppellant [sic] is reminded that Figure 1B is a simple two dimensional line cartoon; proteins are not simple cartoons." Stated differently, what appellants refer to as a three dimensional structure, is simply a two dimensional illustration of the proposed structure of the SR-BI protein.

Further the examiner asserts (Answer, page 19), appellants'

> specification has not correlated any structure other than that encoded by SEQ ID NO[s]: 3 and 7 with a function, yet the claims encompass a vast genus of structures that have no correlation with a function. Particularly, there is no disclosure of a human SR-BI structure to correlate with the required function.

As we understand the examiner's arguments, the examiner recognizes that appellants' specification provides a correlation between the structure of the hamster (SEQ ID NO: 3) and mouse (SEQ ID NO: 7) polynucleotide sequences, and the function of SR-BI. However, while recognizing that the structural limitations[5] present in the claimed invention "provides some constraint on the possible deviation in structure that is allowed" (Answer, page 18), the examiner concludes that the specification fails to provide a correlation between the structure and function of nucleic acid molecules other than mouse and hamster that are encompassed by the claimed genus of nucleic acid molecules. For the following reasons we are not persuaded by the examiner's arguments.

Our appellate reviewing court held in Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002) that a claimed nucleic acid molecule could be described without, necessarily, disclosing its structure. The Enzo court adopted the standard that

> "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed,

[5] The isolated nucleic acid molecule "hybridizes to SEQ ID N[O]s. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA molecule consisting of SEQ ID NO:3 or 7." See e.g., claim 11. Cf. claim 13, which depends from and further limits claim 11 to an isolated nucleic acid molecule that hybridizes "under stringent hybridization conditions at a temperature greater than 25°C below the melting temperature of a perfectly base-paired double-stranded DNA molecule consisting of SEQ ID NO:3.

> relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'"

See id. at 1324, 63 USPQ2d at 1613 (emphasis omitted). Further, the Federal Circuit has held that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

On this record, the examiner recognizes that appellants' specification discloses a correlation between the structure and function of both the hamster and mouse SR-BI nucleic acid molecules. According to the claimed invention[6], the structure of the nucleic acid encoding an SR-BI protein must be such that it hybridizes to SEQ ID N[O]s. 3 and 7 under moderately stringent (claims 11, 12, 19-22 and 44-50) or stringent (claim 13) hybridization conditions. The claimed invention also sets forth the temperature requirement for the hybridization conditions.

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[6] We recognize that claims 44-50 are drawn to methods, however, each method requires the use of an SR-BI nucleic acid as set forth in claim 11. The same is true for claim 20, drawn to a molecule of claim 11 labeled with a detectable label; claim 21, drawn to an expression vector comprising the molecule of claim 11; and claim 22 drawn to a host cell comprising the nucleic acid molecule of claim 11. Accordingly, our discussion of the nucleic acid molecules also applies to claims 20-22 and 44-50.

Further, not only do appellants' claims place a constraint on the structure of the nucleic acid encoding an SR-BI protein, the claims place a constraint on the function of the SR-BI protein that is expressed by such a nucleic acid. Specifically, the claims require that the SR-BI protein has the functional property of selectively binding to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, wherein the binding of acetylated low density lipoprotein to the scavenger receptor protein type BI is inhibited by native low density lipoprotein. See e.g. claim 11.

Upon review of the record, we note that the examiner provides no evidentiary basis to support his conclusion that the description of the hamster and mouse

nucleic acid, along with a disclosure of a correlation between these structures and the function of SR-BI would not be sufficient to describe other nucleic acid molecules sharing a similar structure as defined by the hybridization language set forth in appellants' claimed invention. In contrast, appellants disclose the complete structure of SEQ ID NOs: 3 and 7. In our opinion, the nucleic acid molecules of the claimed genus share the structure of these sequences as defined by the hybridization limitations set forth in appellants' claims, and are required to express a protein that has the functional properties set forth in appellants' claims. The examiner has not adequately explained why this degree of structural similarity is inadequate to "constitute a substantial portion of the genus," as required by Lilly, particularly when the claims require that the nucleic

acid molecules of the genus express a protein having specific functional properties. In this regard, we remind the examiner that he bears the burden of showing that the claims are not adequately described. See In re Alton, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

Further, we remind the examiner that the written description requirement of 35 U.S.C. § 112, first paragraph, does not require a description of the complete structure of every species within a chemical genus. See Utter v. Hiraga, 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."). Accordingly, based on the foregoing, it is our opinion that the evidence of record weighs in favor of appellants.[7]

II. A compound that selectively inhibits binding of lipoprotein to SR-BI:

According to the examiner (Answer, page 5), "claim 49 requires a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI. There is no description of such a compound, and nor could one be envisioned based merely on a desired activity of the compound." In response, appellants assert (Brief, page 41), "[s]upport for this claim is found on page 38, lines 1-11 and page 44, lines 3-22." While the sections cited by appellants discuss inhibition of LDL binding to the SR-BI receptor, the cited

[7] In our opinion, our findings are consistent with the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001), cited with approval in Enzo.

sections do not identify a compound that can be used for this purpose as required by claim 49.

Nevertheless, upon consideration of appellants' specification, we find, for example, that appellants disclose (specification, page 51, lines 7-18),

> [c]ompounds which are effective for blocking binding of the receptor can also consist of fragments of the receptor proteins, expressed recombinantly and cleaved by enzymatic digest or expressed from a sequence encoding a peptide of less than the full length receptor protein. These will typically be soluble proteins, e.g., not including the transmembrane and cytoplasmic regions, although smaller portions determined in the assays described above to inhibit or compete for binding to the receptor proteins can also be utilized.

Accordingly, notwithstanding the examiner's assertion to the contrary, there is no evidence of record to suggest that these compounds would not be within the scope of the compounds set forth in claim 49 that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI. Therefore, we are not persuaded by the examiner's argument.

For the foregoing reasons, we reverse the rejection of claims 11-13, 19-22 and 44-50 under the written description provision of 35 U.S.C. § 112, first paragraph.

Enablement:

I. Library Screening:

The examiner recognizes (Answer, page 10), appellants disclose (specification, page 38) that the nucleic acid molecules having SEQ ID NOs: 3 and 7 can be used to screen libraries for the presence of related receptors.

Nevertheless, the examiner finds (id.), appellants' specification fails to identify which libraries to use, or which tissues to use to make such a library, "that could be expected to yield a gene encoding a protein as large as that of the disclosed scavenger receptor protein type BI proteins." Contrary to the examiner's assertion, page 32 of appellants' specification states "blots using polyclonal antibodies to a cytoplasmic region of SR-BI found that very high levels of protein were present in liver, adrenal tissues, and ovary in mice and rats, but only very low or undetectable levels in either white or brown fat, muscle or a variety of other tissues." Thus, it would appear to us that a person of ordinary skill in the art seeking to isolate SR-BI would use a library from liver, adrenal tissues or ovary. Accordingly, we are not persuaded by the examiner's assertion to the contrary.

In addition, the examiner finds (id.) that library screening

> is further complicated by the fact that the artisan is provided no specific teaching as to parts of the disclosed polynucleotides that should be used as probes and under what conditions should the probes hybridize in order to isolate the required polynucleotides away from the many related polynucleotides that would be expected to hybridize under moderately stringent conditions in libraries constructed from non-rodent species.

However, contrary to the examiner's assertion, page 38 of appellants' specification discloses that libraries are "screened with all or a portion of the nucleotide sequence encoding" SR-BI. Thus, it would appear to us that a person of ordinary skill in the art seeking to isolate SR-BI would screen a library

from liver, adrenal tissues or ovary with, for example, "all"[8] of the nucleotide having SEQ ID NOs: 3 or 7. As set forth in Johns Hopkins Univ. v. CellPro Inc., 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998), "[t]he enablement requirement is met if the description enables any mode of making and using the invention."

We recognize the examiner's comments regarding the use of a "portion" of the nucleotide sequence encoding SR-BI. Specifically, the examiner finds (Answer, bridging sentence, pages 10-11), "[a]t page 38, the specification merely indicates that specific 'regions of interest'[9] are those [portions] of the nucleotide sequence which encode regions of the protein conserved between different receptors; between the same receptors for different species; and with discrete regions of the receptor proteins, e.g. cytoplasmic region, transmembrane region, etc." In the examiner's opinion, however, "[t]he skilled artisan would view these teachings as simply generalized advice and not the specific information required to make probes that can be used to find homologs

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[8] We also note that appellants' specification provides guidance on the use of a "portion" of the nucleotide sequence encoding SR-BI in such a screen. See appellants' specification, page 38, lines 20-33. In addition, we note appellants' statement (Reply Brief, page 8) that "page 18, line 27 to page 19, line 6 [of the specification provides] ... an explicit description of a hybridization procedure in which the isolated hamster SR-BI cDNA is used to produce a 600 base probe ... which is used to probe different cell types from murine tissues and from 3T3 cells."

[9] According to appellants' specification (page 38),

> specific regions of interest are those portions of the nucleotide sequence which encode regions of the protein conserved between different receptors; between the same receptors from different species; and within discrete regions of the receptor proteins: the cytoplasmic region, the transmembrane region, the "stem" regions that may include EFG repeats, collagen like regions alpha-helical coiled regions, or regions having a high density of cysteines (CCP domains), and specific ligand regions. These regions are identified by structural analysis such as that which has been used to generate the schematics in Figures 1A and 1B, using methods routinely available to those skilled in the art.

from other species." We note, however, that appellants' specification discloses the use of the entire nucleotide sequence of SR-BI, e.g., the entire nucleotide sequence set forth in SEQ ID NOs: 3 or 7. We find no argument from the examiner that appellants' specification does not enable the use of the entire sequence of SR-BI to screen a library to obtain a nucleic acid molecule within the scope of the claimed invention.[10] As set forth in Hopkins, "[t]he enablement requirement is met if the description enables any mode of making and using the invention." Accordingly, we are not persuaded by the examiner's arguments.

II. Artificially constructed mutants:

According to the examiner (Answer, bridging paragraph, pages 5-6), "the specification has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 4 or 8, but which still retain a desired property of the polypeptide of SEQ ID NO: 4 or 8."[11] In this regard, the examiner reasons (id.),

> [i]f a variant of the protein corresponding to SEQ ID NO: 4 or 8 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 4 or 8, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 4 or 8. Conversely, if a protein variant of SEQ ID NO: 4 or 8 need not have a disclosed property, then the specification has failed to teach how to use such a variant.

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[10] In this regard, we note appellants' argument (Brief, page 13), "[t]he examiner has provided no evidence that one skilled in the art would not expect to be able to isolate the homologous nucleotide[ ] molecules from any number of other representative widely divergent species."

[11] For clarity, we note that the examiner finds (Answer, page 5), appellants' specification provides an enabling disclosure of nucleic acids having SEQ ID NOs: 3 and 7, which encode polypeptides having SEQ ID NO: 4 or 8 respectively.

In support of his argument, the examiner relies on Bowie and Ngo. Answer, page 8. However, as discussed above, the specification provides an enabling disclosure of isolating nucleic acid molecules within the scope of the claimed invention by screening libraries. As set forth in Hopkins, "[t]he enablement requirement is met if the description enables any mode of making and using the invention."

It may be that the examiner is concerned that the claims include inoperative embodiments. If so, the examiner is directed to Atlas Powder Co. v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984):

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude ... possible inoperative substances...." In re Dinh-Nguyen, 492 F.2d 856, 859-59, 181 USPQ 46, 48 (CCPA 1974)(emphasis omitted). Accord, In re Geerdes, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); In re Anderson, 471 F.2d 1237, 1242, 176 USPQ 331, 334-35 (CCPA 1971). Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. *See* e.g., In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

In this regard, the examiner has provided no evidence that the number of inoperative embodiments encompassed by appellants' claimed invention is so great as to require a person of ordinary skill in the art to experiment unduly in order to practice the claimed invention. Accordingly, we are not persuaded by the examiner's arguments.

III. Tissue Expression:

The examiner asserts (Answer, page 11),

> the tissue specific expression of this [(SR-BI)] mRNA appears to be complex and not well understood. While Northern analysis appeared to indicate that the mRNA was expressed in adipose tissues, [W]estern analysis suggested that it was not – and that a different polynucleotide must have cross-hybridized strongly with the probe in adipose tissues[12] (see page 32, beginning at L25).

As the examiner recognizes (Answer, page 11), appellants' specification discloses that mRNA was detected most abundantly "in fat and was present at moderate levels in lung and liver. There was little expression in the remaining tissues tested, which included kidney, brain, testis, diaphragm, heart, and spleen." See Specification, page 31. Appellants, however, explain why this difference between mRNA expression and protein expression may occur. Specifically, appellants disclose (Specification, bridging paragraph, pages 32-33), "[t]his indicates that the mRNA present in the adipose or steroidogenic tissue actually encodes a close relative of SR-BI, rather than SR-BI, that the SR-

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[12] According to appellants' specification, bridging paragraph, pages 31-33, Northern blot analysis was used to determine the tissue distribution of hamster SR-B1. This analysis revealed that SR-B1

> was most abundant in fat and was present at moderate levels in lung and liver. There was little expression in the remaining tissues tested, which included kidney, brain, testis, diaphragm, heart, and spleen.
>
> ...
>
> In contrast to the studies detecting mRNA encoding SR-B1 ... [Western blots] found that very high levels of protein were present in liver, adrenal tissues, and ovary in mice an rates, but only very low or undetectable levels in either white or brown fat, muscle or a variety of other tissues. ... This indicates that the mRNA present in the adipose or steroidogenic tissue actually encodes a close relative of SR-B1, rather than SR-B1, that the SR-B1 mRN[A] is not translated into protein in fat in rodents and/or that there may be alternative splicing of the SR-B1 gene.

BI mRN[A] is not translated into protein in fat in rodents, and/or that there may be alternative splicing of the SR-BI gene."

As discussed above, appellants disclose that "very high levels of protein were present in liver, adrenal tissues, and ovary in mice and rats, but only very low or undetectable levels in either white or brown fat, muscle or a variety of other tissues." Thus, it would appear to us that a person of ordinary skill in the art seeking to isolate SR-BI would use a library from liver, adrenal tissues or ovary. Accordingly, we disagree with the examiner's assertion (Answer, page 11), "the expression of this polynucleotide appears to be confusing enough in those tissues examined and disclosed in the instant specification – what might be found in a human, for example, is simply beyond reasonable extrapolation." The examiner provides no evidence on this record to suggest that an SR-BI having the properties set forth in appellants' claimed invention could not be isolated from liver, adrenal tissue or ovary. Accordingly, we are not persuaded by the examiner's assertions to the contrary.

IV. Allelic Variants:

The examiner asserts (Answer, page 11), the claims read on allelic variants of SEQ ID NO: 3 or 7. The examiner finds (Answer, bridging paragraph, pages 11-12), however,

> the specification failed to teach where to look for naturally occurring allelic variants of SEQ ID NO: 3 or 7, e.g. no specific disorder or specific phenotype has been asserted to correlate with a naturally occurring allelic variant, such that the artisan might know where to obtain a variant. The specification merely offers the

> skilled artisan the invitation to randomly try to find variants through trial and error sampling of animal populations. Such random trial and error experimentation is unduly burdensome.

The examiner provides no evidence on this record to suggest that a person of ordinary skill in the art would be incapable of routinely obtaining naturally occurring allelic variants of SEQ ID NO: 3 or 7 by screening the tissues disclosed in appellants' specification that express SR-BI mRNA and/or protein. Accordingly, we find the examiner's assertion unsupported by the evidence of record.

V. A compound that selectively inhibits binding of lipoprotein to SR-BI:

With regard to claim 49, the examiner asserts (Answer, page 5), appellants' specification does not provide an enabling description of "a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI, as required by claim 49." In this regard, the examiner asserts (Answer, page 12),

> The specification provides no such compound, but merely an invitation to find such a compound, if such a compound can be found. One highly skilled in the art appreciates that the screening assays described on pages 43-54 are useful for determining whether or not a compound selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI; and although they are useful in the search for such compounds, they do not automatically produce the compounds. The invitation to use these assays to search for compounds having the desired properties is simply an invitation for further research and investigation to randomly sample any and all compounds for the desired activity. Such random experimentation is unduly burdensome.

Upon consideration of appellants' specification, we find, for example, that appellants disclose (specification, page 51, lines 7-18),

> [c]ompounds which are effective for blocking binding of the receptor can also consist of fragments of the receptor proteins, expressed recombinantly and cleaved by enzymatic digest or expressed from a sequence encoding a peptide of less than the full length receptor protein. These will typically be soluble proteins, e.g., not including the transmembrane and cytoplasmic regions, although smaller portions determined in the assays described above to inhibit or compete for binding to the receptor proteins can also be utilized.

Accordingly, notwithstanding the examiner's assertion to the contrary, there is no evidence of record to suggest that these compounds would not be within the scope of the compounds set forth in claim 49 that selectively inhibit binding of lipoprotein to the scavenger receptor protein type BI. As set forth in Hopkins, "[t]he enablement requirement is met if the description enables any mode of making and using the invention." Accordingly, we are not persuaded by the examiner's assertions.

On reflection, for the foregoing reasons we reverse the rejection of claims 11-13, 19-22 and 44-50 under the enablement provision of 35 U.S.C. § 112, first paragraph.

Anticipation:

According to the examiner (Answer, page 16), appellants admit[13] that Calvo provides the nucleotide sequence of the human equivalent of the mouse

[13] See e.g., Declaration, received January 5, 1998, paragraph 2; Accord Declaration, received February 13, 2003, paragraph 8, Calvo reports a nucleic acid and predicted protein sequence for CLA-1, now know to be the human homologue of SR-BI.

and hamster SR-BI. See Calvo, figures 2 and 3, pages 18931-32. In addition, the examiner finds (id.), Calvo teach "the labeled nucleic acid of claim 20 ... [see] [f]igure 5 on pages 18993"; and "host cells comprising the isolated nucleic acid (claim 22) were used in the cloning and sequencing of the nucleic acid, e.g.[,] col[.] 1 of page 18932."

In response, appellants assert (Brief, bridging paragraph, pages 54-55), "the nature of the art is such that upon obtaining the sequence of the ha[mster]SR-BI and the murine SR-BI those of ordinary skill in the art would have found it obvious to obtain the homologs to these nucleic acid molecules...." In this regard, we note that according to the Declaration, received February 13, 2003 (paragraph 8), "[s]creening a human genomic library with the hamster cDNA as a probe under low stringency hybridization conditions would have identified the human homologue for SR-BI (i.e. CLA-1) in exactly the same manner that was routine in the art a decade earlier as demonstrated by Degrave et al." Accordingly, appellants assert (Brief, page 52), they "have clearly demonstrated conception and reduction to practice of the claimed genus prior to Calvo. Therefore Calvo should not be available as prior art to claims 11, 13, 20 and 22." Appellants' assert (Reply Brief, page 11), "[t]o the extent the claims are anticipated by Calvo, then the Declaration under 37 C.F.R. [§] 1.131 must be sufficient to remove Calvo as a reference since the Declaration clearly demonstrates that appellants had cloned, and expressed, and measured the

activity of, SR-BI prior to publication of Calvo." To this the examiner asserts (Answer, page 40), appellants'

> Declaration clearly indicates that prior to the publication of Calvo [a]ppellant[s] was [sic] in possession of only the [c]DNA encoding the hamster SR-BI. As discussed in great detail under the written description rejection, this single cDNA is not sufficient to describe the claimed genus, ... nor is it sufficient to render obvious the human DNA described by Calvo....

As discussed above, we are not persuaded by the examiner's assertion under the written description provision of 35 U.S.C. § 112, first paragraph, that appellants' specification fails to provide an adequate written description of their claimed invention. Accordingly, the issue before us is whether appellants' Declaration under 37 C.F.R. § 1.131 is sufficient to antedate Calvo. In this regard, it is well settled that an anticipatory disclosure, that is not a statutory bar[14], may be removed as a reference against a generic claim by an Declaration under 37 C.F.R. § 1.131 showing prior reduction to practice of as much of the claimed invention as the reference shows. In re Stempel, 241 F.2d 755, 113 USPQ 77 (CCPA 1957). In Stempel the applicant successfully overcame a prior art reference by showing priority to the identical compound taught by the prior art reference. This is, however, not the case before us on this record.

On this record, there is no dispute that appellants had in their possession prior to Calvo, a nucleic acid, specifically the species set forth in SEQ ID NO: 3 of appellants' disclosure, that encodes hamster SR-BI. See Answer, page 40.

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[14] There is no dispute on this record that the 1993 Calvo reference was available as prior art less than one year prior to appellants' June 23, 1994 filing date. Thus, Calvo is not a statutory bar against appellants' claimed invention.

From this single species, appellants' intend to indirectly antedate Calvo's teaching of a nucleic acid encoding CLA-1, a species of human SR-BI. In this regard, we note that "[p]riority as to a genus may indeed be shown by prior invention of a single species...." In re Zletz, 893 F.2d 319, 323, 13 USPQ2d 1320, 1323 (Fed. Cir. 1989), citations omitted. Accordingly, as set forth in In re Clarke, 356 F.2d 987, 992, 148 USPQ 665, 669-70 (CCPA 1966),

> the rule for antedating references is not limited to fact situations where the inventor can show priority as to the identical compound described in the reference. It seems that in an appropriate case an applicant should not be prevented from obtaining a patent to an invention where a compound described in a reference would have been obvious to one of ordinary skill in the art in view of what the affiant proves was completed with respect to the invention prior to the effective date of the reference.

Stated differently, "[w]hen that species of the generic invention which has been completed prior to the effective date of the reference would make obvious to one of ordinary skill in the art the species disclosed in the reference, the reference may be said to have been 'indirectly antedated.'" In re Rainer, 390 F.2d 771, 774, 156 USPQ 334, 336-37 (CCPA 1968); See also In re Spiller, 500 F.2d 1170, 1177, 182 USPQ 614, 619 (CCPA 1974) (appellants need show priority with respect to only so much as to render the claimed invention obvious to a person of ordinary skill in the art in view of the reference.).

Accordingly, we must determine whether appellants' cDNA encoding hamster SR-BI, the species of appellants' generic invention that was completed prior to Calvo, would have rendered Calvo's CLA-1 (now known to be human SR-BI) sequence obvious to one of ordinary skill in the art. There can be no

doubt that such a determination implicates In re Deuel, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995), in "that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs." Accord, In re Bell, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed, Cir. 1993). However, as set forth in Deuel,

> a prior art disclosure of a process reciting a particular compound or obvious variant thereof as a product of the process is, of course, another matter, raising issues of anticipation under 35 U.S.C. Section 102 as well as obviousness under Section 103. Moreover, where there is prior art that suggests a claimed compound, the existence, or lack thereof, of an enabling process for making that compound is surely a factor.

In this regard, we note, as set forth in In re Goldgaber, 41 USPQ2d 1172, 1176 (Bd. Pat. App. & Int. 1995), "[w]e find nothing intrinsically wrong ... in the application of methodology in rejecting product claims under 35 USC [§] 103, depending on the particular facts of the case, the manner and context in which methodology applies, and the overall logic of the rejection." Therefore, by analogy, there is nothing intrinsically wrong in appellants' reliance on the application of methodology to demonstrate that their hamster nucleic acid would render the sequence taught by Calvo obvious to a person of ordinary skill in the art. On this record, this is what appellants have done.

There is no dispute on this record that appellants had in their possession a cDNA that encodes hamster SR-BI. On this record, appellants have averred that by using "the hamster cDNA sequence to generate a radiolabeled probe and

screen a mouse 3T3-LI adipocyte library for the corresponding mouse SR-BI sequence using established protocols in the art" they were able to isolate the mouse form of SR-BI, the sequence of which is disclosed in appellants' specification as SEQ ID NO: 7. See Declaration filed under 37 C.F.R. § 1.132, paragraph 6. Accordingly, in our opinion, appellants' have placed the key in the lock of the door of success and all that remains for a person having ordinary skill in the art is to turn the key and arrive at the human SR-BI taught by Calvo. Cf. Goldgaber, at 41 USPQ2d at 1175. The examiner places no evidence on this record that a person of ordinary skill in the art would have obtained a human SR-BI nucleic acid that was different than that disclosed by Calvo.

Based on this evidence, it is our opinion that appellants have provided sufficient evidence to demonstrate that they were in possession of the genus of nucleic acid molecules encoding a scavenger receptor protein type BI which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, wherein the binding of acetylated low density lipoprotein to the scavenger receptor protein type BI is inhibited by native low density lipoprotein, and the isolated nucleic molecule hybridizes to SEQ ID N[O]s. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA molecule consisting of SEQ ID NO[s]: 3 and 7. See e.g., claim 11. Accordingly, we find appellants' evidence sufficient to antedate the Calvo reference with regard to the rejection of claims 11, 13, 20 and 22.

Regarding claim 19, as we understand it, claim 19 is not drawn to a particular sequence and reads on, for example, genomic DNA and cDNA. Thus, claim 19 is drawn generically to a nucleic acid molecule that encodes a human scavenger receptor. Stated differently, claim 19 is drawn to a human subgenus of the genus of nucleic acid molecules set forth in claim 11.[15] Therefore, for the reasons set forth above, it is our opinion that the evidence of record is sufficient to antedate the Calvo reference with respect to claim 19.

For the foregoing reasons we reverse the rejection of claims 11, 13, 19, 20 and 22 under 35 U.S.C. § 102(a) as anticipated by Calvo.

Obviousness:

According to the examiner (Answer, page 16), "[c]laim 21 requires an expression vector comprising the polynucleotide of claim 11." In this regard, the examiner finds, Calvo "teach the polynucleotide of claims 11 in Figures 2 and 3 encoding the CLA-1 protein." Id. According to the examiner (Answer, page 17), when expressed as a fusion protein with CD36, the carboxy terminal of Calvo's CLA-1 protein "was expressed predominantly in the plasma membrane." The examiner finds (id.), based on the plasma membrane localization of the CD36/CLA-1 protein, Calvo "concluded that native CLA-1 would also be expressed in the membrane (see page 18933, col. 2)."

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[15] Therefore, we find that the principle set forth in In re Gladrow, 160 USPQ 674 (CCPA 1969) (Clarke does "not stand for the proposition that a showing of prior invention of a species [(e.g., species X)] can antedate a reference disclosing another species [(e.g., species Y)] when it is the reference species [(species Y)] for which a claim is sought."), does not apply to the facts on this record.

Based on this reasoning, the examiner finds (id.),

> it would [have] be[en prima facie] obvious to one of ordinary skill in the art ... [at the time the invention was made] to express the CLA-1 protein by incorporating the cDNA described therein into an expression vector and heterologous host by employing those methods which are routine in the art at the time the invention was made to permit the quantitative production of CLA-1 and to facilitate its characterization at the molecular level with a reasonable expectation of success.

According to the examiner (id.), "[t]he motivation to do so was to conduct assays for binding partners of the polypeptide as suggested in col[.]2[,] page 1893 [sic] of Calvo...."

We note, however, that Calvo teaches (page 18934, bridging sentence, columns 1 and 2) that "[s]o far it is difficult to envisage a function for CLA-1, but if its location on the plasma membrane is confirmed, one could speculate on the basis of its structural homology to CD36 that CLA-1 could act as a receptor for extracellular products" [emphasis added]. In this regard, we remind the examiner, if the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is not sufficient to render structurally similar claims prima facie obvious because there is no motivation for one of ordinary skill in the art to make the reference compounds, much less any structurally related compounds. In re Stemniski, 444 F.2d 581, 586, 170 USPQ 343, 348 (CCPA 1971).

Nevertheless, even if a person of ordinary skill in the art knew how to use an expression construct containing Calvo's CLA-1, as discussed above, it is our opinion that appellants declaration under 37 C.F.R. § 1.131 was sufficient to

antedate the human nucleic acid molecule taught by Calvo. As the examiner recognizes (Answer, page 17), once the nucleic acid for the human SR-BI protein was known it would have been prima facie obvious to a person of ordinary skill in the art to place the protein encoding portion of the nucleic acid into an expression vector and heterologous host by employing those methods which are routine in the art at the time the invention was made to express the human SR-BI protein. According to appellants' 131 Declaration prior to Calvo's publication date they inserted their hamster cDNA into a plasmid, which was then transfected into COS cells to screen for endocytosis of acetylated low density lipoprotein (AcLDL). See 131 Declaration at paragraph 3.

Accordingly, we reverse the rejection of claim 21 under 35 U.S.C. § 103 as being unpatentable over Calvo.

REVERSED

William F. Smith
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

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